BCH 405 – REGULATION OF METABOLIC PROCESSES

SYNOPSIS

The relationship of Krebs cycle to protein, carbohydrate, lipid and nucleic acid metabolism. Integration of metabolic pathways illustration of regulation of linear and branched metabolic pathways using specific example.

Turnover rates and metabolic pools catabolite repression, end-product repression, the lactose and arabinose operons. Identification of different regulatory mechanisms in metabolic pathways.

INTRODUCTION

Metabolism can be defined as the sum of all the enzyme-catalysed reactions that take place in cells. Metabolism is highly coordinated, purposeful activity in which many sets of interrelated multi-enzyme systems participate, exchanging both matter and energy between the cell and its environment. Metabolism has four specific functions:

(1) To obtain chemical energy from fuel molecules or from absorbed sunlight.

(2) To convert exogenous nutrients into the building blocks, or precursors, of macro-molecular cell components.

(3) To assemble such building blocks into proteins, nucleic acids, lipids and other cell components.

(4) To form and degrade bio-molecules required in specialised functions of cells.

Metabolism can be divided into 2 phases – Catabolism and Anabolism. Catabolism is the degradative phase of metabolism in which complex nutrient molecules (lipids, carbohydrates and proteins) are broken down to simpler end-products such as $C0_2$, H_20 and NH_3 and is accompanied by the synthesis of ATP. Anabolism refers to biosynthetic processes in which simple precursor molecules are enzymatically converted into the molecular

components of cells, such as nucleic acids, proteins, lipids and polysaccharides. Biosynthesis requires the input of ATP which is provided by catabolism. There is also often a requirement for reducing power in the form of NADPH.

It is seen from all these considerations that whether it is catabolism or anabolism, a metabolic pathway consists of a series of enzyme catalysed reactions that convert a substrate into a product. The individual reactions of many such pathways have been elucidated using the following techniques:

(1) Identification of intermediates which accumulate upon the addition of specific inhibitors of the pathway;

(2) The addition of possible intermediates of the pathway (since their conversion to the product confirms the role).

(3) The addition of radioactively labeled substrate (or intermediates) and the study of the distribution of the label in intermediates and products.

(4) The separation of the enzymes of the pathway and the elucidation of the chemistry of each reaction in isolation.

The results of these investigations have now been collated into metabolic maps.

Stages of Metabolism.

Although metabolism involves hundreds of different compounds and enzymes, 3 stages of metabolism are recognized.

Draw Diagram

Stage 1: The nutrient macro-molecules are broken down into their respective building blocks – Proteins will yield amino acids, polysaccharides give rise to carbohydrate units that are convertible to glucose and lipids are broken down into glycerol and fatty acids and other components.

In stage II of metabolism, the many different products of stage 1 are collected and converted/degraded again into simpler metabolic intermediates. Thus, hexoses, pentoses and glycerol are degraded via the 3-carbon intermediate pynuvic acid to yield a single Z-carbon species, acetyl CoA. The various fatty acids and amino acids are broken down to form acetyl CoA and a few other end products. The combustion of the acetyl groups of acetyl CoA by the nitric acid cycles and oxidative PO4 lation to produce $C0_2$ and H_20 represent stage 3 of catabolism. $C0_2$ and H_20 are the ultimate waste products of aerobic catabolism.

Biosynthesis also takes place in 3 stages. Small precursor molecules are generated in stage 3, then converted in stage 2 into building block molecules, which are finally assembled into macro-molecules in stage 1, For e.g. biosyn of proteins begins in stage 3 with the formation of certain α-Keto acids, which are precursors of the α-amino acids. In stage 2, the α-Keto acids are ammated by amino-group donors to form α-amino acids. Finally in stage 1, the amino acids are assembled into polypeptide chains.

Catabolic pathways have diffuse beginning (starting from many fuel molecules) but converge into a final route in stage 3. Anabolic pathways diverge; they start from a few precursors in stage 3 and as they proceed through stage 2 and stage 1, they branch and diverge, leading to formation of many different kinds of biomolecules.

Converging Pathways of Catabolism

Diverging pathways of Biosynthesis

Differences between catabolism and anabolism

(1) They are not the reverse of each other
(2) They are independently regulated
(3) They often take place in different locations in the cells (compartmentalization β-oxidation-mutochondria syn of fatty acids – cytosol.

Cellular regulation of metabolic pathways

Metabolic pathways can be linear, e.g. glycolysis or can be cyclic, e.g. TCA. In general, the rate of catabolism is controlled not by the conc. of nutrients available in the environment of the cell, but by the cell's need for energy in the form of ATP. Similarly, the rate of biosynthesis of cell components is also adjusted to immediate needs. However, the regulation of a metabolic pathway may occur at several levels.

(1) The reaction rate of each enzymatic reaction si a function of the pH and the intracellular concs. of its substrates products and cofactor which are pry-elements in the regulation of enzyme activity.

(a) Substrate availability – Any metabolic pathway could in theory at least, be regulated very simply by the availability of substrate. A reduction insubstrate conc. will decrease the activity of the enzyme (provided it is not saturated with substrate) and this could result in

a decreased flux through the pathway. Similarly, an increase in (S) could stimulate the path-way. In general however, the constancy of the internal environment of the animal and the cell, as regards the substrates of metabolic pathways implies that such regulatory mechanisms are not common in higher animals. However, a typical, e.g. of control by substrate availability is that by plasma conc of fatty acids. The conc of plasma fatty acids appears to play a fundamentally impt. role in the regulation of their oxidation by various tissues and in turn their oxidation can modify the rate of carbohydrate utilization by the animal. IN such a situation, if the conc. of the fatty acid is known to be regulatory, emphasis then shifts from the metabolic pathway that accounts for plasma fatty acid conc./transport to the factors responsible for changes in fatty acid conc.

(b) Cofactor availability – Some what similar to control by substrate availability. However, substantial inhibition of enzyme activity (and therefore the rate of the metabolic pathway) could be achieved only if the conc. of the cofactor was reduced to very low levels. This may only be possible if the cofactor is specific for the particular pathway in question and is not required for other pathways. Although such specific is uncommon, a typical, e.g. will be carmitine, a cofactor involved in fatty acid oxidation.